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Review

Percutaneous coronary intervention in diabetic patients with non-ST-segment elevation acute coronary syndromes

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Key pathophysiologic mechanisms of diabetes-related coronary disease include inflammation and a prothrombotic state. In the setting of non-ST-segment elevation acute coronary syndromes diabetic patients are at high risk for subsequent cardiovascular events. At the same time, they derive greater benefit than non-diabetic counterparts from aggressive antithrombotic therapy, early coronary angiography, and stent-based percutaneous coronary intervention. The mainstays of antithrombotic therapy for diabetic patients undergoing percutaneous revascularization include aspirin, clopidogrel, platelet glycoprotein IIb/IIIa receptor antagonists, and heparin or low-molecular-weight heparin. Despite dramatic reduction in restenosis conferred by drug-eluting stents, diabetic patients remain at increased risk for repeat revascularization. More efforts are needed both in terms of local drug elution as well as systemic pharmacologic therapies to further contain the excessive neointimal proliferation that characterizes the diabetic response to vascular injury.

Introduction

It is estimated that sixteen million people in the US have diabetes mellitus, a condition that may shorten life expectancy by up to 15 years.[1] Atherosclerosis accounts for about 80% of all deaths, of which roughly three-quarters are attributable to coronary artery disease and the remainder to cerebrovascular or peripheral vascular events. As the prevalence of diabetes is estimated to double by the year 2025, the burden of cardiovascular disease associated with this condition will dramatically increase.[2] Of particular concern is the observation that although over the last two decades cardiovascular mortality has considerably declined a similar trend has not been observed among diabetic patients.[3] Pathologic and angiographic studies support the notion that diabetic patients have more diffuse and advanced coronary artery disease than non-diabetics.[4] In addition to coronary disease, diabetic cardiovascular involvement is characterized by higher prevalence of hypertension, heart failure, peripheral vascular and cerebrovascular disease, and nephropathy.

In the setting of non-ST-segment elevation acute coronary syndromes (ACS), diabetes was found to be an independent predictor of mortality.[5] In addition, this condition has been associated with worse outcomes following both coronary artery bypass grafting (CABG)[6] and percutaneous coronary intervention (PCI).[7] The purpose of this review is to summarize relevant biologic and metabolic abnormalities, adjunctive treatments, and outcomes of diabetic patients undergoing PCI, in particular in the setting of ACS.

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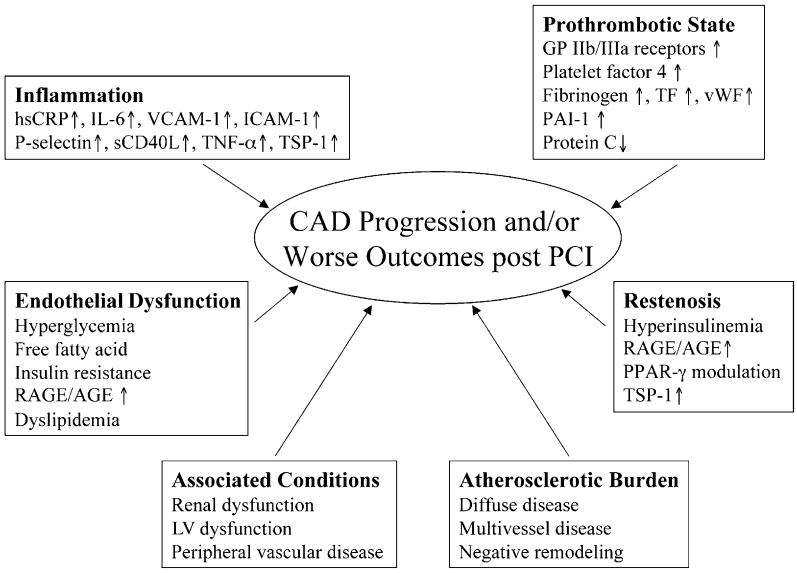

Fig. 1 Selected factors potentially affecting coronary artery disease (CAD) progression and/or outcomes following percutaneous coronary intervention (PCI) among diabetic patients. hs-CRP=high-sensitivity C-reactive protein; IL-6=interleukin-6; VCAM-1=vascular sell adhesion molecule-1; ICAM-1=intracellular adhesion molecule-1; sCD40L=soluble CD40 ligand; TNF-α=tumour necrosis factor-α; TSP-1=thrombospondin-1; RAGE=receptor for advanced glycation end-products (AGE); GP=glycoprotein; TF=tissue factor; vWF=von Willebrand factor; PAI-1=plasminogen activator inhibitor-1; LV=left ventricular; PPAR-γ=peroxisome proliferator-activated receptor-γ.

Cardiovascular impact of biologic and metabolic diabetic abnormalities

Several biological and metabolic abnormalities may confer vulnerability to diabetic individuals for cardiovascular events and potentially influence the outcomes following revascularization (Fig. 1). One putative pathway is the oxidation of amino groups by glucose, which ultimately results in the formation of advanced glycation end-products (AGE).[8] Processes induced by augmented AGE production include endothelial dysfunction, subendothelial cellular proliferation and matrix expression, cytokine release, macrophage activation, and expression of adhesion molecules.[8,9] Diabetic endothelial dysfunction may be caused by a variety of additional factors including hyperglycaemia, increased free fatty acid, altered lipoproteins, insulin resistance, and hypertension.[10,11]

Prothrombotic state

The observation that diabetic patients have a hypercoagulable state is based both on the increased risk of thrombotic events and on laboratory abnormalities. An angioscopic study performed in ACS patients revealed that plaque ulceration and intracoronary thrombus was more frequent among diabetic patients that among nondiabetics.[12] Similarly, the incidence of thrombus was found to be higher in atherectomy specimens from patients with diabetes than in those of non-diabetic counterparts.[13] Diabetic individuals have increased platelet activation and aggregation to shear stress and platelet agonists.[14] Increased levels of procoagulant agents such as fibrinogen, tissue factor, von Willebrand factor, platelet factor 4, factor VII, and decreased concentrations of endogenous anticoagulants such as protein C and antithrombin III have been documented.[15] Elevated levels of plasminogen activator inhibitor-1 (PAI-1) may impair endogenous tissue plasminogen activator-mediated fibrinolysis.[16] Finally, platelets of diabetic individuals are larger and have an increased numbers of glycoprotein (GP) IIb/IIIa receptors per platelet.[17] Despite the evidence of a prothrombotic diabetic state, the exact mechanisms linking characteristics laboratory findings to the initiation and progression of the atherosclerotic process remain elusive.

Inflammatory state

Inflammation has been related not only to acute cardiovascular events but also to initiation and progression of atherosclerosis.[18] The final pathway of many acknowledged cardiovascular risk factors including diabetes appears to be the inducement of an inflammatory state, which may be exaggerated in the setting of ACS. Although we commonly consider white blood cells to be the principal mediators of inflammation, the key role of platelets has recently been demonstrated.[19,20] Among other, platelets are the primary source of the circulating/soluble form of CD40 ligand (sCD40L), a protein that is among the most important triggers of the cascade of inflammatory cytokines and adhesion molecules, therefore linking inflammation and thrombosis.[21]

The interaction between the diabetes and inflammation appears particularly complex.[22] Although it is plausible that metabolic disturbances associated with this condition trigger vascular inflammation, the converse may also be true. Accordingly, C-reactive protein (CRP) was shown to independently predict the risk of

Table 1 Clinical outcomes patients undergoing percutaneous coronary intervention in the TARGET trial according to diabetic status.[32] Reproduced with permission

Time	Event	Diabetes *n*=1117	No diabetes *n*=3692	*P*
30 days	Death	4 (0.4%)	18 (0.5%)	0.577
	Non-fatal MI[a]	59 (5.3%)	237 (6.4%)	0.174
	Death/MI	62 (5.5%)	248 (6.7%)	0.172
	Urgent TVR[b]	5 (0.4%)	31 (0.8%)	0.191
	Death/MI/urgent TVR	65 (5.8%)	261 (7.1%)	0.153
6 months	Death	19 (1.7%)	32 (0.9%)	0.019
	Non-fatal MI	72 (6.4%)	278 (7.5%)	0.231
	Death/MI	88 (7.9%)	298 (8.1%)	0.824
	Any TVR	115 (10.3%)	287 (7.8%)	0.008
	Death/MI/TVR	182 (16.3%)	519 (14.1%)	0.082
1 year	Death	28 (2.5%)	60 (1.6%)	0.056

[a]MI=myocardial infarction.
[b]TVR=target vessel revascularization.

later developing type 2 diabetes.[23] Inflammatory parameters elevated in diabetes include CRP, Il-6, tumour necrosis factor alfa (TNα), and sCD40L (Fig. 1).[24,25] In addition, this condition is associated with an increased expression of adhesion molecules such as endothelial (E)-selectin, serum vascular cell adhesion molecule-1 (VCAM-1) and intracellular adhesion molecule-1 (ICAM-1).[26] The link between inflammation and outcome can be outlined among other by the observations that elevation of high-sensitivity CRP, interleukin-6 (IL-6), or serum VCAM-1 have been associated with increased mortality in patients with coronary artery disease.[27] The morphological substrate of increased vascular inflammatory activity can be derived by an analysis of coronary atherectomy specimen of ACS patients, showing that tissue from diabetic patients exhibited a larger content of lipid-rich atheroma and a more pronounced macrophage infiltration compared with specimen of nondiabetics.[13]

Percutaneous coronary intervention

While in-hospital and 30-day outcomes after PCI in diabetic patients are comparable to those of nondiabetics,[7,28] large-scale registries have shown that diabetes remained in recent years an independent predictor of long-term mortality and need for repeat revascularization.[7,29] Underlying mechanisms that may be related to this inferior outcome include endothelial dysfunction, prothrombotic state, greater propensity for restenosis and negative vascular remodelling, increased protein glycosylation and vascular matrix deposition. These mechanisms appear to be potentiated by hyperglycaemia and hyperinsulinaemia.[30]

Although, the placement of intracoronary stent reduced the incidence of restenosis, diabetic patients remained at higher risk for subsequent target vessel revascularization (TVR) compared with nondiabetics.[31] Nevertheless, the Do Tirofiban and ReoPro Give similar Efficacy outcomes Trial (TARGET) demonstrated that modern PCI, based on stenting and administration of multiple antiplatelet agents, substantially improved outcomes in this high-risk patient population.[32] The TARGET trial randomized patients at the time of stent-based PCI to the GP IIb/IIIa antagonists tirofiban or abciximab in addition to aspirin, clopidogrel, and periprocedural unfractionated heparin. When compared with non-diabetic patients (*n*=3692), those with diabetes (*n*=1117) had similar 30-day event rates (Table 1). No difference in major adverse cardiac events (MACE) at 6 months was observed among the two groups, though diabetic patients had more TVR (10.3% vs 7.8%, *P*=0.008) and higher mortality (1.7% vs 0.9%, *P*=0.019) than non-diabetic patients. At 1 year, a trend towards increased mortality in the diabetic group persisted (2.5% vs 1.6%, *P*=0.056). Although the mortality data are concerning, the overall low event rates observed in the TARGET trial demonstrates that in diabetic patients with suitable coronary anatomy stent-based PCI with triple antiplatelet therapy performs satisfactorily. The low TVR rate reproduced on a larger scale the single digit event rate (8.1%) observed among diabetic patients randomized to the abciximab-stent arm (*n*=162) of the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial.[33]

Restenosis

Restenosis in diabetic patients is characterized by heightened proliferative response and increased vascular matrix deposition. Mechanisms that may play a role include the interaction of the receptor for AGE (RAGE) and its ligand, the peroxisome proliferator-activated receptor (PPAR)-γ and thrombospondin-1 (TSP-1). RAGE, a multiligand member of the immunoglobulin superfamily of cell surface molecules, is expressed at low levels in homeostasis but is upregulated at the site of vascular injury, particularly within the expanding neointima.[34] Animal studies have shown that blockade of RAGE resulted in significantly decreased neointimal proliferation, migration, and expression of extracellular matrix proteins.[34] Similar findings were described in the RAGE null mice.[34] With respect to diabetes, RAGE have been shown to be over-expressed after balloon injury in the

Zucker rat model and again blockade of RAGE/ligand interaction significantly reduced vascular smooth muscle cell proliferation and neointimal formation.[35]

Thrombospondin-1 (TSP-1) is a multifunctional protein that interacts with a variety of matrix proteins and cell surface receptors and among other induces vascular smooth muscle cell proliferation and prevents endothelial cell growth.[36] The clinical relevance of this molecule can be derived from a genetic link demonstrated between TSP-1 and premature atherosclerosis.[37] Recently, an increased expression of this protein in the vascular wall of diabetic Zucker rats has been observed, potentially linking diabetes, atherogenesis, and accelerated restenosis.[38]

Early invasive versus conservative strategy

The role of early revascularization with either CABG or PCI in diabetic patients with stable symptoms is currently being tested in the Bypass Angioplasty Revascularization Investigation (BARI)-2D.[39] In the setting of non-ST-segment elevation ACS, the positive impact of an early invasive strategy among diabetics can be derived from subgroup analyses of large-scale randomized trials. The Fragmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) study randomized with a 2×2 factorial design around 2500 patients to an invasive or conservative strategy and unfractionated heparin or dalteparin.[40] Allocation to the invasive strategy was associated with a significant 22% reduction in death or myocardial infarction (MI) at 6 months. Among diabetic patients the relative risk reduction was similar but, due to higher events rates, the absolute benefit was greater (6.2%) compared with non-diabetics (2.3%). At 1 year, diabetic patients undergoing early invasive therapy had a 38% reduction in the relative risk of death (7.7% vs 12.5%), albeit not reaching statistical significance due to the small sample size (n=299).[41]

In the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 trial,[42] an early (i.e., within 48 h) invasive strategy was associated with a significant 22% reduction in the relative risk of death, MI, or rehospitalization for ACS at 6 months compared with an early conservative strategy.[42] All patients were treated with aspirin, clopidogrel and tirofiban. Diabetic patients had a greater benefit than non-diabetics from the early invasive assessment both in terms of absolute (7.6% and 1.8%, respectively) and relative 6-months event reduction (27% and 13%, respectively) (Fig. 2).

Therefore, an early invasive assessment and if appropriate revascularization should be considered the strategy of choice for diabetic patients with ACS. The question how early should coronary angiography be performed has no definitive answer. Within a small (n=131) randomized trial, The Value of First Day Angiography/Angioplasty In Evolving Non-ST segment Elevation Myocardial Infarction: An Open Multicenter Randomized Trial (VINO), same day (mean 6.2 h) angiography and if needed revascularization was very effective compared with a conservative strategy (6-month death or MI rate 6.2% and 22.3%, respectively;

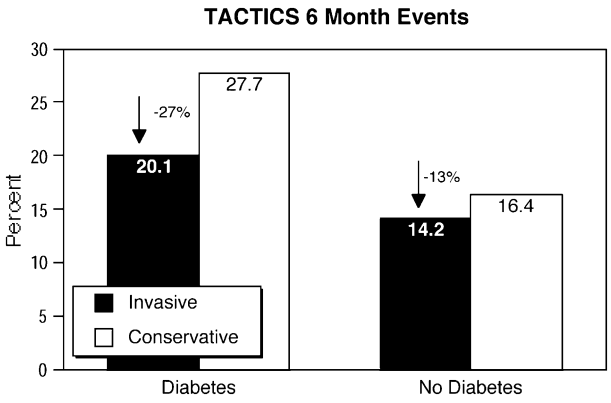

Fig. 2 Event rates at 6 months (death, myocardial infarction, or rehospitalization for acute coronary syndromes) in the TACTICS trial[42] according to diabetes status.

P<0.001).[43] Similarly, the Intracoronary Stenting with Antithrombotic Regimen COOLing-off (ISAR-COOL) study found a benefit of an immediate invasive strategy with an average time to catheterization of 2 h compared with a delayed invasive strategy (3–5 days) despite aggressive antithrombotic treatment (i.e., aspirin, clopidogrel, tirofiban, and unfractionated heparin). At 30 days the death or MI rate was 5.9% in the immediate angiography group and 11.6% among delayed assessment group.[44] Importantly, the difference in the MI rate was entirely due to events occurring prior to revascularization. Although data specifically relating to diabetic patients are missing, these findings suggest that despite potent platelet inhibition it is rational to proceed with the earliest cardiac catheterization.

Coronary artery bypass surgery in acute coronary syndromes

The only randomized comparison between CABG with PCI in patients with ACS is the Percutaneous Coronary Intervention Versus Coronary Artery Bypass Graft Surgery for patients with Medically Refractory Myocardial Ischemia and Risk Factors for Adverse Outcomes with Bypass (AWSOME) trial.[45] This study enrolled patients with medically refractory unstable angina and at high-risk for CABG. Among 2431 patients identified, 454 were considered acceptable for both PCI and CABG, 1650 patients were not deemed to be candidate for both therapies and entered a physician-directed registry, and the 327 who were considered candidate for both treatment but refused randomization entered a patient-choice registry. Overall diabetes prevalence was 31%. The respective CABG and PCI 3-year survival rate for diabetic patients were 72% and 81% for randomized patients (Fig. 3), 85% and 89% for patient-choice registry patients, and 73% and 71% for the physician-directed registry patients.[46] None of the differences was statistically significant. These results should be interpreted with caution, since from both a surgical (left internal mammary artery used as arterial conduit in 70% of cases) and an interventional

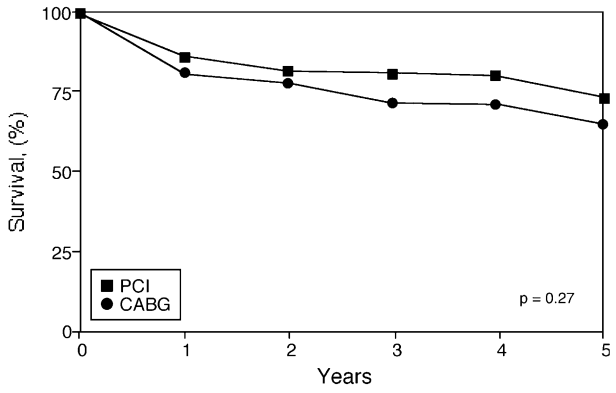

Fig. 3 Long-term survival among diabetic patients with acute coronary syndromes randomized to percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) in the AWSOME trial.[46] Reproduced with permission.

perspective (stents used in 54% and GP IIb/IIIa antagonists in 11% of cases) the way patients were revascularized in the study may not comply with current standards. Nevertheless, CABG and PCI appear to be comparable options for diabetic patients with ACS and the choice of revascularization should be made individually based on coronary anatomy, ventricular function, age, and comorbidities.

Adjunctive pharmacologic treatment

Clopidogrel

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial randomized patients with ACS primarily medically managed to aspirin or aspirin and clopidogrel. Diabetic patients (*n*=2840) derived only a modest benefit from the combined treatment for 3 to 12 months (death, MI, or stroke rate 14.2% vs 16.7%; *P*=ns) (Fig. 4). Among patients undergoing PCI the benefit of the combined antiplatelet therapy was somehow less marked (relative risk 0.77) among diabetic patients compared with non-diabetics (RR 0.66).[47] The Clopidogrel for the Reduction of Events During Observation (CREDO) trial addressed a broader patient population, namely individuals referred for a planned PCI or deemed to be at high likelihood for requiring PCI.[48] Patients were randomized to a loading dose of clopidogrel followed by 12-month therapy or no loading dose and clopidogrel treatment for 1 month. Among 560 diabetic patients, the benefit of pre-treatment/prolonged clopidogrel therapy was modest compared to the one observed among 1556 non-diabetics (relative risk reduction 11% and 33%, respectively).[48] Nevertheless, clopidogrel should be administered, preferably prior to coronary angiography, in addition to aspirin to all diabetic patients with ACS unless contraindicated.

Glycoprotein IIb/IIIa receptor antagonists

Despite increased baseline platelet aggregability, the administration of abciximab has been shown to achieve a similar degree of platelet inhibition among diabetic and non-diabetic patients undergoing PCI.[49] Intravenous GP IIb/IIIa receptor inhibitors and intracoronary stents have markedly reduced the early hazard in diabetic patients undergoing PCI. In the EPISTENT trial abciximab halved the risk of death, MI, or urgent revascularization at 30 days among stented patients with diabetes (from 12.1% to 5.6%).[50] The observed event rate was comparable to that of abciximab-treated non-diabetic patients (5.2%). A pooled analysis of the early abciximab trials demonstrated a survival benefit at 1 year among diabetic patients receiving the GP IIb/IIIa inhibitors compared with placebo (mortality 4.5% vs 2.5%; *P*=0.031).[51]

While the overall impact of GP IIb/IIIa receptor inhibitors in the medical management of non-ST-segment elevation ACS has been modest,[52] a mortality benefit has been detected among diabetic patients. The meta-analysis of the diabetic populations (*n*=6458) enrolled in the six large-scale GP IIb/IIIa inhibitor ACS trials detected a 26% mortality reduction associated with the use of these agents at 30 days compared with placebo, from 6.2% to 4.6% (*P*=0.007) (Fig. 5). These findings were reinforced by a statistically significant interaction between treatment and diabetic status. Glycoprotein IIb/IIIa receptor inhibition was associated with similar proportionate reduction in mortality for patients treated with insulin and those on diet or oral hypoglycaemic drugs. Even more striking was the benefit among diabetic patients undergoing PCI. In this group of patients 30-day mortality was reduced by 70%, from 4.0% to 1.2% (*P*=0.002) (Fig. 6).

Further studies are needed to define whether the preferential benefit observed with the administration of these potent platelet inhibitors is related to diabetes-associated conditions such as increased platelet activation, heightened inflammation, or to more diffuse atherosclerosis with subsequent propensity for microvascular embolization. Even without elucidation of the mechanism, the data are compelling enough that the administration of GP IIb/IIIa inhibitors should be considered standard of care for all diabetic patients presenting with ACS. With respect to whether one agent may be preferable over another in diabetic patients, subgroup analysis of the TARGET trial demonstrated that the small-molecule tirofiban and the antibody fragment abciximab led to overall similar outcomes among patients undergoing PCI.[32] In particular, no difference was observed in this thus far unique head-to-head comparison in terms of TVR or late mortality, suggesting that the non-GP IIb/IIIa properties of abciximab do not translate into a long-term clinical benefit among diabetic patients.

GPIIb/IIIa receptor antagonists: still necessary in the clopidogrel era?

In ACS patients, GP IIb/IIIa receptor antagonists have been shown to be most effective within high risk groups such as troponin positive, patients undergoing PCI, and those with high clinical risk score.[52,53] The same may not true for clopidogrel, which conferred in the CURE trial similar benefit across the spectrum of patient risk[54]

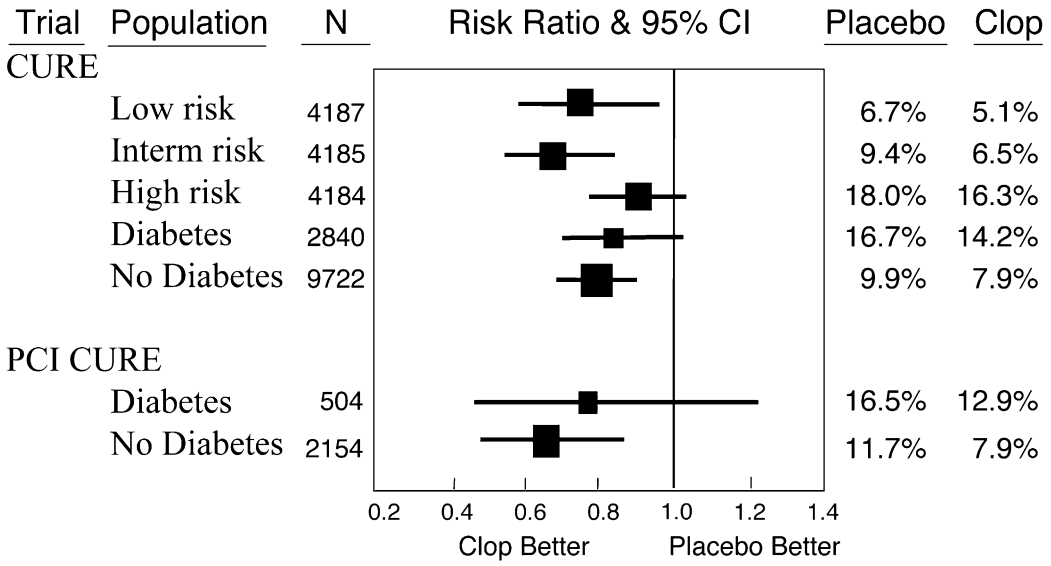

Fig. 4 Impact on the combined end-point of death, myocardial infarction, or stroke of clopidogrel given for 3–12 months vs placebo according to clinical risk stratification or diabetes status in the CURE trial[65] and in the subgroup of patients who underwent percutaneous coronary intervention during index hospitalization (PCI CURE).[47] All patients received aspirin. CI=confidence interval; clop=clopidogrel; interm=intermediate.

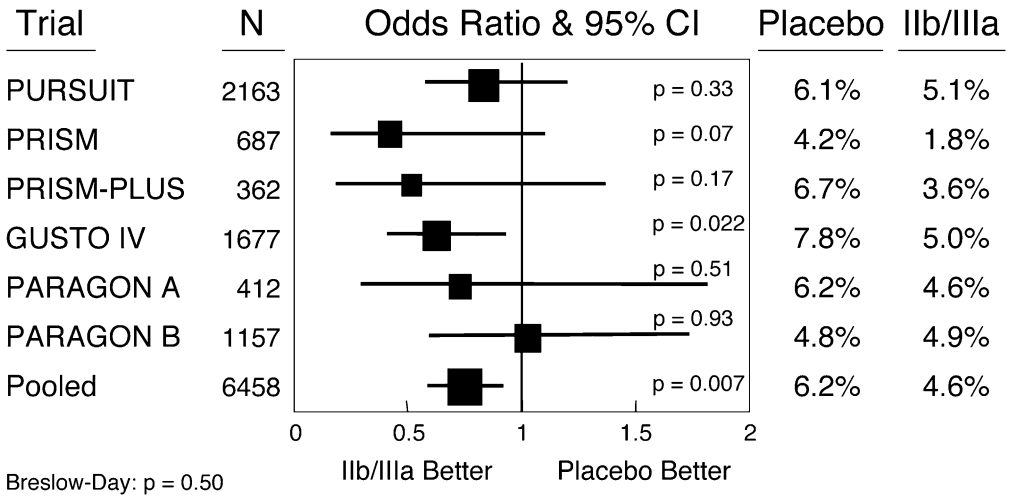

Fig. 5 Odds ratio with 95% confidence intervals (CI) and corresponding *P*-values for treatment effect on 30-day mortality among diabetic patients with acute coronary syndromes. Values to left of 1.0 indicate a survival benefit of platelet glycoprotein IIb/IIIa inhibition (IIb/IIIa).[55] Reproduced with permission.

revascularization strategies (Fig. 4).[47] Importantly, the preferential benefit of GP IIb/IIIa receptor inhibitors among diabetic patients, both in the setting of PCI[33] and ACS[55] could not be replicated with clopidogrel. Finally, the excellent results obtained among diabetic patients undergoing PCI in the TARGET trial were obtained with triple antiplatelet therapy (i.e., aspirin, clopidogrel pretreatment, and GP IIb/IIIa antagonists).[32] Recently, a provocative preliminary report suggested that among patients receiving 600 mg clopidogrel >2 h prior to the intervention abciximab may nor confer additional benefit.[56] However, this study targeted low-risk patients and both ACS patients and diabetics on insulin were excluded. Therefore, triple antiplatelet regimen should be considered state-of-the art for diabetic patients with ACS.

Combination of GP IIb/IIIa receptor inhibitors and low-molecular-weight heparin

The Aggrastat to Zocor (A-to-Z) study was the first clinical trial powered to address clinical endpoint assessing the use of low-molecular-weight heparin (LMWH) and GP IIb/IIIa receptor inhibitors in non-ST-elevation ACS. In addition to aspirin and tirofiban patients were randomized enoxaparin or weight-adjusted unfractionated heparin. About 60% of the almost 4000 patients enrolled

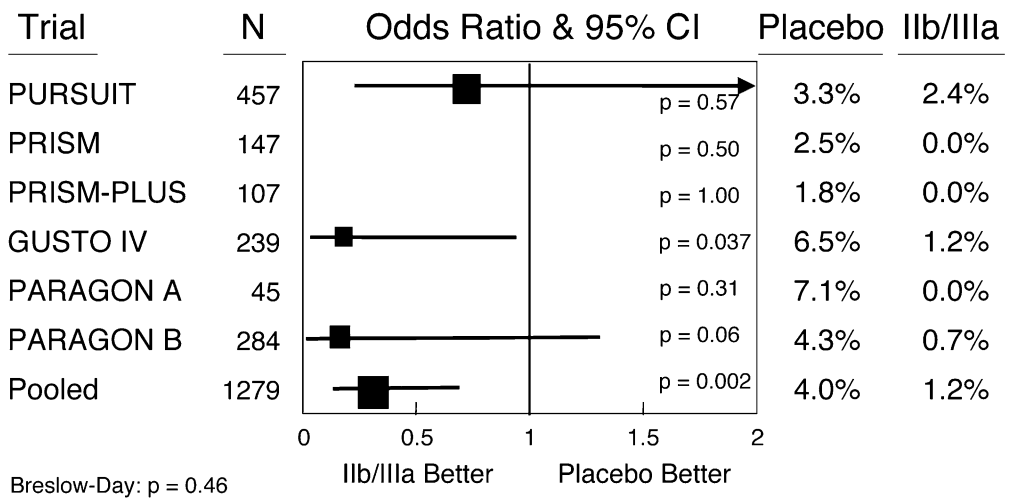

Fig. 6 Odds ratio with 95% confidence intervals (CI) and corresponding *P*-values for treatment effect on 30-day mortality among diabetic patients with acute coronary syndromes undergoing percutaneous coronary intervention. Values to left of 1.0 indicate a survival benefit of platelet glycoprotein IIb/IIIa inhibition (IIb/IIIa).[55] Reproduced with permission.

underwent early angiography. Overall, the two strategies were equivalent in terms of 7-day death, MI, or refractory ischaemia, with a trend towards more bleeding in the enoxaparin group.[57] The ischaemic event rates in diabetics did not differ among the two strategies. More information on the safety and efficacy of enoxaparin in ACS patients undergoing early invasive assessment will be gathered in the ongoing Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial,[58] which is comparing enoxaparin to unfractionated heparin in 8000 patients treated with early invasive strategy. Currently, both heparin and LMWH should be considered antithrombotic drugs of choice for diabetic patients with ACS undergoing PCI.

Evolving therapies

Drug-eluting stents

The Randomized Study with the Sirolimus-Eluting Bx-Velocity in the Treatment of Patients with de novo Native Coronary Artery Lesions (SIRIUS)[59] randomized 1101 patients to the sirolimus-eluting or bare metal stent and confirmed the extraordinary reduction in restenosis previously reported in the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL) trial.[60] Among diabetic patients enrolled in the SIRIUS trial (n=279), the sirolimus-eluting stent was associated dramatic reduction in restenosis compared with the bare stent (6.9% vs 22.3%, P<0.001). The relative risk reduction for restenosis was of the same magnitude among diabetic and non-diabetic patients (70–80%). Due to higher event rates, the absolute benefit derived within the diabetics population was greater than among non-diabetics (154 and 111 restenosis prevented per 1000 patients, respectively). Despite these impressive findings, several observations suggest that diabetic restenosis may be particularly resilient. In the SIRIUS trial diabetes remained an independent predictors of poor angiographic and clinical outcome among patients undergoing sirolimus-eluting stent implantation. In addition, the restenosis rate among diabetic patients with lesions >15 mm in vessels <2.5 mm was as high as 23.7%. Finally, in the small group of patients treated with insulin (n=82), the benefit in terms of restenosis of drug-elution was modest (35.0% vs 50.0%; P=0.38).

The preliminary results the TAXUS IV trial have been recently presented. In this study, 1314 patients with single de novo lesions of 10–28 mm length and a reference vessel diameter of 2.50–3.75 mm were randomized to slow-release paclitaxel-eluting stent or bare metal stent. Angiographic follow-up at 9 months was available for roughly three-quarters of the population enrolled in the angiographic substudy. Among non-diabetic patients (n=422), the binary restenosis rate in the analysis segment, defined as the stented segment plus 5 mm at the proximal and distal edges of the stent, was 8.5% in the paclitaxel-eluting stent group and 24.4% in the control group (P<0.0001). The corresponding restenosis rates for diabetic patients (n=136) were 6.4% and 34.5% (P<0.0001). The inhibition of restenosis was profound and achieved statistical significance among both diabetic patients on oral hypoglycaemic drugs (n=89) (restenosis rate 5.8% and 29.7%, respectively) and those on insulin (n=47) (restenosis rate 7.7% and 42.9%, respectively).[61] Clinical trials dedicated to diabetic patients are warranted to address potential differences in efficacy among agents used for local drug delivery.

Thiazolidindiones and RAGE/AGE suppression

All the major cells in the vasculature express the PPAR-γ receptor, including endothelial cells, smooth muscle cells, and monocytes/macrophages. Thiazolidindiones

(TZD) bind with high affinity to PPAR-γ receptor to enhance insulin-mediated glucose transport into adipose tissue and skeletal muscle. Troglitazone, rosiglitazone, and pioglitazone inhibit vascular smooth muscle cells proliferation in vitro at drug levels therapeutic for anti-diabetic therapy.[62] In a small randomized trial, the administration of troglitazone following coronary stenting was associated with a reduction of restenosis on intravascular ultrasound follow-up.[63] However, the drug was subsequently withdrawn from the market following reports of severe hepatotoxicity. Recently, a positive effect on restenosis has been reported with rosiglitazone.[64] Among 93 diabetic patients, randomization to TZD for 6 months post-PCI was associated with a significant restenosis reduction compared with placebo (12% vs 47%, $P<0.001$). Clinical trials powered to assess restenosis are needed before these agents can be recommended as routine oral anti-diabetic drug therapy post-PCI.

Based on the previously described animal studies showing striking neointimal suppression after vessel injury associated with the suppression of the RAGE/AGE complex both in the mice and in Zucker rats,[34,35] this interaction is the next logic target for restenosis prevention, particularly in diabetics. Currently, studies are being performed in pigs and efforts are being made to produce a small molecule RAGE inhibitor.

Conclusions

Inflammation and a prothrombotic state are key pathophysiologic mechanisms of diabetes-related coronary disease. In the setting of ACS diabetic patients are at higher risk for subsequent cardiovascular events but at the same time derive greater benefit from aggressive therapy than the non-diabetic counterparts. The mainstays of acute-phase therapy include triple antiplatelet therapy (i.e., aspirin, clopidogrel, and GP IIb/IIIa receptor antagonist), heparin or LMWH, early invasive assessment and, if appropriate, stent-based PCI. Coronary artery bypass grafting may be a valid alternative in patients with complex coronary anatomy, particularly in the setting of impaired left ventricular function. Despite dramatic reduction in restenosis conferred by drug-eluting stents, diabetic patients remain at increased risk for repeat revascularization. Therefore, more efforts are needed both in terms of local drug elution as well as systemic pharmacologic therapies to further contain the excessive neointimal proliferation that characterizes the diabetic response to vascular injury.

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